REMARKS

Claims 1-6 were pending in the present application. By this Amendment, Applicants have amended claim 1. Claims 2-3 and 5-6 have been canceled without prejudice to the right to pursue the canceled subject matter in a future continuing application. New claims 7 and 8 have been presented. Support for the claim amendments and the new claims can be found throughout the specification and claims as originally filed. Specifically, support can be found, *inter alia*, at pages 7-9 in the specification. The present Amendment does not introduce any new matter and thus, its entry is respectfully requested. Upon entry of the present Amendment, claims 1, 4, and 7-8 will be pending and under examination.

The January 11, 2006 Office Action

Examiner's Claim Rejections Under 35 U.S.C. §112, second paragraph

Claims 1-6 were rejected as allegedly being indefinite under 35 U.S.C. §112, second paragraph, in their recitation of the term "survival time" as seen in the preamble of claim 1. In the Examiner's view, this phrase renders the claims unclear because the claimed method does not in fact predict an absolute survival time, but rather a relative time of survival for a subject possessing a mutation versus a subject not possessing a mutation. The Examiner therefore has suggested clarifying the claim to read "relative time of survival" instead of "survival time." Claims 1-6 also were rejected as being indefinite in their use of the term "reduced survival" (in claim 1, part b). According to the Examiner, this term renders the claims unclear because the claims do not provide a standard for comparison. The Examiner has suggested clarifying claim 1 to include, at the end, the clause "as compared to the time of survival of a subject having

multiple sclerosis but not having the mutation."

In response, without conceding the correctness of the Examiner's position, but to expedite allowance of the subject application, Applicants have amended claim 1. Applicants believe the claim amendments fully address and overcome the Examiner's concerns. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-6 under 35 U.S.C. §112, second paragraph.

Examiner's rejections Under 35 U.S.C. §112, first paragraph—enablement and written description

Claims 1-6 were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking full enablement. Specifically, the Examiner has acknowledged that the claims are enabled for a method for predicting time of survival in human subjects having multiple sclerosis (MS) and possessing the CCR5 delta 32 deletion mutation, as compared to an MS patient not having the mutation, but has asserted that the claims are not enabled for analysis of non-human subjects, or for the use of any other CCR5 mutation to predict survival time. The Examiner's full rationale is set forth at pages 3-8 of the Office Action. Essentially, the Examiner has taken the position that the broadest claims encompass the detection (in any human or nonhuman subject) of any type of mutation in the CCR5 gene, including any type of single base or multi-nucleotide transition, or transversion, insertion, deletion, or any type of gene rearrangement anywhere within the coding, non-coding, or regulatory regions of the gene. The Examiner has therefore concluded, in light of the claim breadth and other factors, such as unpredictability in the art and a purported limited amount of guidance in the specification, that the amount of experimentation required of one of

ordinary skill in the art to practice the invention as claimed would be undue.

Claims 1-6 also were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking adequate written description. The Examiner has again noted the breadth of the claims and has asserted that the CCR5 delta 32 deletion mutation taught in the specification is insufficiently representative of the broad range of potential mutations encompassed by the claims. The Examiner stated that the application does not demonstrate the nature of any CCR5 mutations from human subjects other than the CCR5 delta 32 deletion, nor any explanation of how any CCR5 mutation is functional with respect to prediction of survival time of a subject having MS. The Examiner also asserted that the specification provides no relevant identifying characteristics of a mutation that would suggest any particular mutation (other than the specifically recited CCR5 delta 32 mutation) would be useful in predicting shorter relative survival time in a subject with MS. Thus, the Examiner has concluded that one of ordinary skill in the art would not believe that the inventors had possession of the invention, as claimed, at the time the application was filed.

In response, without conceding the correctness of the Examiner's position, but to expedite allowance of the subject application, Applicants have amended the claims to recite human subjects and the specific CCR5 delta 32 deletion mutation, subject matter the Examiner has acknowledged is adequately described in and fully enabled by the specification. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections of claims 1-6 under 35 U.S.C. §112, first paragraph.

Examiner's Claim rejections under 35 U.S.C. §103

The Examiner rejected claims 1-3 as allegedly being obvious under 35 U.S.C. §103(a) over Barcellos, et al., in view of Midgard, et al., both of which were cited in the previously filed IDS. Claims 4-6 were rejected as being obvious over Barcellos, in view of Midgard, and further in view of Cohen, et al (U.S. Pat. No. 6,265,546).

In rejecting the claims, the Examiner has asserted that Barcellos teaches that age of onset of MS was approximately 3 years later in patients carrying the CCR5 delta 32 deletion. The Examiner has acknowledged, however, that Barcellos does not specifically teach that the CCR5 delta 32 deletion correlates to a reduced survival time in subjects having MS versus subjects having MS who do not possess the deletion. The Examiner has further asserted that Midgard, et al. teaches that the shortest survival is in patients with a high age of onset. The Examiner has taken the position that it would have been obvious for one of ordinary skill in the art to have combined the method and results of Barcellos with the teachings of Midgard to arrive at the conclusion that the presence of the CCR5 delta 32 deletion mutation in a subject with MS is predictive of a shorter survival time versus a subject that does not possess the mutation. The Examiner has relied on the Cohen reference for its general teaching that whole blood is a useful source of DNA for genotyping analysis.

In response, Applicants respectfully traverse the Examiner's obviousness rejections. Applicants assert that the Examiner's analysis is fundamentally flawed. The Examiner's position necessarily relies first on a conclusion that there is a link between the presence of the mutation in an MS patient and a later age of onset of the disease (as allegedly established by Barcellos), and second, that a later age of onset of the disease correlates with a shorter survival time (as allegedly

established by Midgard). Therefore, the Examiner's ultimate conclusion that presence of the mutation correlates with shorter survival time cannot be supported unless the first link in this chain is established in the art. The art of record, however, establishes no such link. Indeed, the Examiner himself acknowledged in his enablement rejection (see page 7 of the Office Action) that the art is unclear in this regard. Specifically, the Examiner stated:

> The prior art specific to the CCR5 delta 32 deletion mutation and relative time of survival also indicates the unpredictability of using the presence of the CCR5 delta 32 deletion as an indicator of a shorter relative time of survival. Sellebjerg et al (2000) (as cited in the IDS) teaches an analysis of the CCR5 delta 32 mutation as it correlates to several parameters of disease course in subjects with MS. Sellebjerg et al teaches that the age of onset of disease is lower in patients carrying the delta 32 deletion mutation of the CCR5 gene than in the remaining patients (p.100-Results *3.1 CCR5 Δ32 in patients and control subjects*). . . . Midgard et al teaches that the shortest survival is in patients with a high age at onset (p.418 - Results; table 1). Taken together, these references would indicate that the delta 32 deletion mutation of the CCR5 gene is indicative of a <u>longer</u> relative survival time. (Underlining added).

Thus, the Examiner's own words acknowledge that there is prior art which, if considered in combination with the art cited in the obviousness rejection would cast doubt on the very conclusions relied on to sustain the rejection. The present specification in fact also refers to this failure in the art to establish a reliable correlation between presence of the mutation and age of onset of the disease. Paragraph [0009], for example, notes the same inconsistent teachings of Sellebjerg and Midgard to which the Examiner referred, as well as the teachings from a third reference, Bennetts, which offers yet another possible alternative, i.e., that presence of the mutation makes no difference. Thus, because one of ordinary skill in the art could not have

believed with any reasonable degree of certainty that presence of the mutation correlates with age of onset, one then could not reasonably have reached the conclusion that the presence of the mutation correlates with survival time. It is the Applicants' invention that has established this link, thereby overcoming the uncertainty that was present in the art at the time of the invention. For at least these reasons, Applicants' claims are not rendered obvious by the cited art. Accordingly, Applicants respectfully request reconsideration and withdrawal of the Examiner's rejection under 35 U.S.C. §103. .

In view of the above amendments and remarks, Applicants believe all of the Examiner's rejections set forth in the January 11, 2006 Office Action have been fully overcome and the application is in condition for allowance. The Examiner is invited to telephone the undersigned if it is deemed to expedite allowance of the subject application.

Respectfully submitted,

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